1: AIDS Res Hum Retroviruses. 1997 Jul 20;13(11):933-43. Related Articles, Links

A humanized form of a CD4-specific monoclonal antibody exhibits decreased antigenicity and prolonged plasma half-life in rhesus monkeys while retaining its unique biological and antiviral properties.

Reimann KA, Lin W, Bixler S, Browning B, Ehrenfels BN, Lucci J, Miatkowski K, Olson D, Parish TH, Rosa MD, Oleson FB, Hsu YM, Padlan EA, Letvin NL, Burkly LC.

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Certain monoclonal antibodies (MAbs) directed against CD4 can efficiently block HIV-1 replication in vitro. To explore CD4-directed passive immunotherapy for prevention or treatment of AIDS virus infection, we previously examined the biological activity of a nondepleting CD4-specific murine MAb, mu5A8. This MAb, specific for domain 2 of CD4, blocks HIV-1 replication at a post-gp120-CD4 binding step. When administered to normal rhesus monkeys, all CD4+ target cells were coated with antibody, yet no cell clearance or measurable immunosuppression occurred. However, strong anti-mouse Ig responses rapidly developed in all monkeys. In the present study, we report a successfully humanized form of mu5A8 (hu5A8) that retains binding to both human and monkey CD4 and anti-AIDS virus activity. When administered intravenously to normal rhesus monkeys, hu5A8 bound to all target CD4+ cells without depletion and showed a significantly longer plasma half-life than mu5A8. Nevertheless, an anti-hu5A8 response directed predominantly against V region determinants did eventually appear within 2 to 4 weeks in most animals. However, when hu5A8 was administered to rhesus monkeys chronically infected with the simian immunodeficiency virus of macaques, anti-hu5A8 antibodies were not detected. Repeated administration of hu5A8 in these animals resulted in sustained plasma levels and CD4+ cell coating with humanized antibody for 6 weeks. These studies demonstrate the feasibility of chronic administration of CD4-specific MAb as a potential means of treating or preventing HIV-1 infection.

PMID: 9223409 [PubMed - indexed for MEDLINE]

1: AIDS Res Hum Retroviruses. 2002 Jul 20;18(11):747-55.

Related Articles, Links

A humanized, nondepleting anti-CD4 antibody that blocks virus entry inhibits virus replication in rhesus monkeys chronically infected with simian immunodeficiency virus.

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Therapeutic approaches that interfere with viral entry hold promise in preventing or treating HIV infection. Hu5A8, a humanized monoclonal antibody against CD4, was previously shown to inhibit HIV and SIV replication in vitro and was safely administered to rhesus monkeys without depleting CD4(+) T cells. This antibody completely suppressed replication of six different SIVmac 251 primary isolates in vitro. Twice weekly administration of 3-mg/kg doses of hu5A8 for 2 to 4 weeks to SIV-infected rhesus monkeys resulted in sustained plasma antibody levels of > or =20 microg/ml during treatment and 5- to 50-fold decreases in plasma viremia, although suppression of viral replication was transient. Two of three treated monkeys developed antibody responses against the administered monoclonal antibody. Loss of antiviral effect was not temporally associated with anti-hu5A8 antibody responses or due to activation of CD4(+) T cells by hu5A8. However, SIV isolated after hu5A8 treatment was approximately 5-fold more resistant to suppression by hu5A8 than SIV isolates obtained from the same monkeys before treatment. The rapid development of resistance may have resulted from SIV variants that infect cells by a CD4-independent mechanism. These results support the overall concept of anti-CD4 monoclonal antibody treatment to suppress AIDS virus replication in vivo while demonstrating important issues as to its clinical feasibility.

PMID: 12167266 [PubMed - indexed for MEDLINE]

1: Toxicology. 2002 Apr 2;172(3):191-203.

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ELSEVIER SCIENCE FULL-TEXT ARTICLE

Development of anti-CD4 MAb hu5A8 for treatment of HIV-1 infection: preclinical assessment in non-human primates.

Boon L, Holland B, Gordon W, Liu P, Shiau F, Shanahan W, Reimann KA, Fung M.

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The anti-CD4 MAb 5A8 is a potent inhibitor of CD4-mediated infection of HIV-1. CD4 is obligatory for infection with primary HIV-1 isolates. Humanized 5A8 (hu5A8) was constructed to reduce the potential immunogenicity and enhance the in vivo half-life when used in humans. hu5A8 is a molecularly engineered human IgG4 antibody retaining the binding and functional properties of the murine version of 5A8 (mu5A8). This humanized MAb has been shown to be very effective in inhibiting HIV-1 infection of human CD4+ T cells and macrophages in vitro and to reduce viral load in rhesus monkeys chronically infected with simian immunodeficiency virus (SIV). 5A8 was evaluated in a good laboratory practice (GLP)-compliant tissue cross-reactivity study on human (three donors/37 tissues) and rhesus monkey (two donors/37 tissues) tissues. hu5A8 bound to the surface of human T cells and macrophages, but only to T cells from rhesus monkeys. The antibody did not cross react with other tissues. The highly identical staining patterns of hu5A8 in human and rhesus monkey tissues support the use of rhesus monkeys as a preclinical model for humans. In a GLP-compliant safety study in rhesus monkeys, weekly administration of hu5A8 at 5 mg/kg or 25 mg/kg for 8 weeks was shown to be safe and well tolerated in all monkeys. Although hu5A8 induced anti-hu5A8 antibody response in healthy rhesus monkeys, it was not immunogenic in chimpanzees. Together, the results from these preclinical studies support the studies of the anti-HIV-1 effect of hu5A8 in HIV-1 infected individuals.

PMID: 11893418 [PubMed - indexed for MEDLINE]

1: AIDS Res Hum Retroviruses. 1995 Apr;11(4):517-25. Related Articles, Links

In vivo administration of CD4-specific monoclonal antibody: effect on provirus load in rhesus monkeys chronically infected with the simian immunodeficiency virus of macaques.

Reimann KA, Cate RL, Wu Y, Palmer L, Olson D, Waite BC, Letvin NL, Burkly LC.

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Since monoclonal antibodies (MAb) specific for CD4 are potent inhibitors of HIV and SIV replication in vitro, we explored their potential usefulness in vivo as an AIDS therapy. The anti-CD4 MAb 5A8 binds to domain 2 of the CD4 molecule and inhibits virus replication and virus-induced cell fusion at a postvirus binding step. Administration of this MAb to normal rhesus monkeys coats all circulating and lymph node CD4 cells and induces neither CD4 cell clearance nor measurable immunosuppression. In the present study, monkeys chronically infected with the simian immunodeficiency virus of macaques (SIVmac) had stable levels of SIVmac provirus in PBMC prior to treatment as measured by a quantitative polymerase chain reaction technique. Six infected monkeys treated with anti-CD4 MAb demonstrated a significant decrease in SIVmac provirus level after 9 days. Of these monkeys, 3 had > 800 CD4 cells/microliter and developed strong antimouse Ig responses that prevented further treatment. The remaining 3 monkeys had < 800 CD4 cell/microliter and failed to develop antimouse Ig antibody responses. When treatment was continued for 12-21 days in these monkeys, a sustained or further decrease in SIVmac provirus load occurred over the extended treatment period. Four monkeys that received a control MAb of irrelevant specificity for 9-22 days showed either no significant change or a transient increase in SIVmac provirus. Thus, the passive administration of anti-CD4 MAb may exert a specific antiviral effect in controlling immunodeficiency virus infection in vivo.

PMID: 7632466 [PubMed - indexed for MEDLINE]

1: AIDS Res Hum Retroviruses. 1993 Mar;9(3):199-207. Related Articles, Links

In vivo administration to rhesus monkeys of a CD4-specific monoclonal antibody capable of blocking AIDS virus replication.

Reimann KA, Burkly LC, Burrus B, Waite BC, Lord CI, Letvin NL.

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Monoclonal antibodies (mAbs) specific for CD4 are potent inhibitors of HIV replication in vitro. These agents may be useful prophylactically or in chronic HIV infection if they can be administered without inducing immunosuppression. In the present study, we explored the safety of a CD4-specific murine mAb in rhesus monkeys. The mAb 5A8, which binds to domain 2 of the CD4 molecule, inhibits AIDS virus replication noncompetitively at a postvirus binding step. This antibody, which had a similar affinity for rhesus monkey and human CD4 cells, efficiently inhibited in vitro replication of both HIV-1 and the simian immunodeficiency virus of macaques. A single 3-mg/kg injection of mAb 5A8 into normal rhesus monkeys coated all circulating and lymph node CD4 cells for 4-6 days. CD4 cells were not cleared from circulation nor was the CD4 molecule modulated from the lymphocyte surface. In fact, administration of mAb 5A8 resulted in an approximately one- to twofold increase in absolute number of circulating CD4 cells. Repeated administration in normal rhesus monkeys resulted in CD4 lymphocyte coating with mAbs for > 9 days without CD4 cell clearance or modulation. While coated with mAbs, PBLs of these monkeys retained normal in vitro proliferative responses to mitogens and these animals generated normal humoral responses in vivo to tetanus toxoid. Loss of cell coating with mAbs in normal monkeys corresponded to the appearance of anti-mouse immunoglobulin antibodies. Thus, administration of certain anti-CD4 mAbs capable of blocking HIV replication can achieve coating of the entire CD4 cell pool in rhesus monkeys without inducing significant cell loss or immunosuppression.

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